# Preoperative Versus Postoperative Misoprostol in Elective Cesarean Section to Reduce Blood Loss

## *A double-blinded Randomized Clinical Trial*

***Thesis***

*Submitted for partial fulfillment of Master Degree in*
***Obstetrics and Gynecology***
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# List of Abbreviations

| | |
|---|---|
| **AFI** | Amniotic Fluid Index |
| **Aptt** | Activated Partial Thrombin Time |
| **AUC** | Area Under Curve |
| **BUN** | Blood Urea Nitrogen |
| **c-AMP** | Cyclic Adenosine Monophosphate |
| **CBC** | Complete Blood Count |
| **$C_{max}$** | Peak Concentration |
| **COX** | Cyclooxgenase |
| **CS** | Cesarean Section |
| **DIC** | Disseminated intravascular coagulopathy |
| **EP** | Prostaglandin receptor for prostaglandin E |
| **Hb** | Hemoglobin |
| **Hct** | Hematocrit |
| **I.U.** | International Unit |
| **INR** | International Normalized Ratio |
| **LFT's** | Liver Function Tests |
| **LSCS** | Lower Segment Cesarean Section |
| **M.W.** | Molecular Weight |
| **MPA** | Misoprostol Acid |
| **NSAIDs** | Non Steroidal Anti Inflammatory Drugs |
| **NVD** | Normal Vaginal Delivery |
| **PG** | Prostagalndins |
| **PPH** | Post Partum Hemorrhage |
| **PT** | Prothrombin Time |
| **RBCs** | Red Blood Cells |
| **$T_{max}$** | Peak Time Concentration |
| **VBAC** | Vaginal Birth after section |
| **WHO** | World Health Organization |

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# PREOPERATIVE VERSUS POSTOPERATIVE MISOPROSTOL IN ELECTIVE CESAREAN SECTION TO REDUCE BLOOD LOSS A DOUBLE-BLINDED RANDOMIZED CLINICAL TRIAL

Protocol of thesis
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# Introduction

Cesarean sections (CS) are the most common major surgical interventions among women. Cesarean sections can leadto serious fetal or maternal complications, including primary postpartum hemorrhage (PPH) **(Mathai et al., 2013).**

Intra-partum and early postpartum blood loss are also increased in conjunction with CS. The American Congress of Obstetricians and Gynecologists (ACOG) defines PPH as the loss of more than 500 mL of blood after vaginal delivery and the loss of 1000 mL or more after CS **(ACOG, 2006).**

Postpartum hemorrhage is a leading cause of maternal mortality and morbidity, especially in low-resource countries. The incidence of CS is increasing and the average blood loss during CS (1000 mL) is double the amount lost during vaginal delivery (500 mL)**(Magann et al., 2005).**

The most successful method for reducing PPH, active management of the third stage of labor (AMTSL), requires prophylactic utero-tonic drugs. The utero-tonic drugs used include oxytocin, ergometrine malate and combinations of the two all of which must be administered by injection **(Langenbach, 2006).**

Misoprostol is affordable and widely available, can be easily administeredvia multiple routes, and has a good safety profile if properly administeredand monitored, all of which makes it an alternative treatment option of PPH in low-resource countries**(Dermanet al., 2006).**

Misoprostol, a synthetic prostaglandin with utero-tonic properties, has been proposed as an alternative strategy for

prevention of PPH in settings where oxytocin use is not handy. It has important advantages over oxytocin, including the potential for oral administration and a long shelf life at room temperature ***(Tang et al., 2007).***

Misoprostol can be administered sublingually, enabling a more rapid onset of action and greater bioavailability by avoiding first-pass metabolism ***(Emer and Garret, 2010).***

No clinically significant adverse hematological, endocrine, biochemical, immunological, respiratory, ophthalmic, platelets or cardiovascular effects have been found with misoprostol. Diarrhea is the major adverse reaction that has been reported consistently with misoprostol, but it is usually mild and self-limiting. Nausea and vomiting may also occur and will resolve in 2 to 6 hours ***(Henriques et al., 2007).***

# Aim of work

The aim of the work is to compare the efficacy of preoperative versus postoperative administration of sublingual misoprostol in reducing blood loss in elective cesarean section.

# Research question

In women undergoing elective cesarean section is preoperative administration of sublingual better than postoperative administration in reducing blood loss.

# Research hypothesis

Preoperative administration of misoprostol is better than postoperative administration in reducing blood loss in elective cesarean section.

**Null hypothesis,**

There is no difference in preoperative or postoperative misoprostol administration regardingreducing blood loss in elective cesarean section.

# Patient and methods

## Study Design

Prospective double-blinded placebo-controlled randomized clinical trial.

## Setting

The study will be conducted at Ain-Shams University Maternity Hospital from June 2016 till December 2016.

### Sample Size Justification

Sample size was calculated setting the power at 80% and the two-sided confidence level at 95%. No data comparing preoperative versus postoperative sublingual misoprostol is to-date published. However, data from a previous relevant study ***(Ragab et al., 2015)***, comparing preoperative versus postoperative rectal misoprostol showed a significantly lower rates of additional utero-tonic agents [39.7% vs. 21.8%, p=0.01]. Calculation according to these values produces a minimal sample size of 105 in each group. Assuming a drop-out rate of 15%, a total sample size of 240 women is needed, to be randomized into two groups.

## Population of study

240 women candidate for elective cesarean section, 1/2 of them will receive preoperative sublingual 400 microgram of misoprostol **(Sigma)** and other 1/2 will receive postoperative sublingual 400 microgram misoprostol **(Sigma)**.

## Inclusion criteria

1. Patients booked for elective cesarean section.
2. Singleton pregnancies.
3. Full term pregnancies (GA 37- 42 Wks).
4. Age (18-40 yrs).
5. body mass index (BMI)(20-30)$Kg/m^2$.

## Exclusion criteria

1. Contraindication to spinal anesthesia.
2. Blood dyscrasias.
3. Large fibroids.
4. Multiple pregnancies.
5. Overdistended uterus eg. Hydramnios.
6. Pre-eclampsia.
7. Marked maternal anemia (Preoperative hemoglobin <9 gm/dl).
8. Previous history of PPH.
9. Contraindications to prostaglandin therapy (e.g. history of severe bronchial asthma or allergy to misoprostol.
10. Placenta previa.
11. Previous myomectomy.
12. Extreme of BMI (<20 or >30$Kg/m^2$).

## Methodology

All patients will be subjected to the following:

**1-History:** including obstetric history with determination of gestational age from last menstrual period in regular menstrual cycles & history of any risk factors for PPH (e.g. bleeding disorders).

**2-Physical examination:** including general examination, blood pressure before and after operation, assessment of maternal health, obstetric abdominal examination for: fundal level, fetal presentation, estimating fetal weight and scars of previous operations.

**3-Investigations:**

A-Ultrasound will be done for gestational age confirmation through fetal biometry, detection of fetal presentation and exclusion of major congenital malformations, or placenta previa, estimation of the amniotic fluid index (AFI) & Amniotic fluid volume (AFV). The AFI will be calculated by dividing the uterus into four quadrants, by the lineanigra into right and left quadrants and the umbilicus into upper and lower quadrants. The maximum vertical diameter of AF in each quadrant will be measured in centimeters, and the 4 measurements will be added together to calculate the AFI (cm). The AFV (ml) will be estimated by multiplying AFI (cm) by 30 (k) ***(Phelan et al., 1987).***

B- Hemoglobin (Hb) level and hematocrit will be obtained before cesarean section for each case.

**4-Surgeon:** cesarean section would be done by a senior registrar who performed at least 300 cesareansections before the start of the study.

All women who doesn't meet the inclusion and exclusion criteria will be excluded from the study.
Informed verbal and written consent will be obtained from each case before participation in the study after explanation of the benefits, risks and aim of the study.

## Methods of randomization

To insure that everyone has the chance of participation, randomization will be guided by computer generated list, Double blinding will be done by one of the supervisors who will be the only one to know the key ,thus the investigator and the patient will not know is it the drug or the placebo. Placebo will be the same in size, color and shape to the original drug, the placebo and misoprostol will be put in 240 numbered closed envelopes according to the table of random numbers and an envelope will be allocated to each patient accordingly. By the end of the study the investigator will be informed by the randomization to be tabulated later on.

## Allocation concealment

Sequentially numbered, opaque, sealed envelopes will be used.

**The patients will be divided into 2 groups**

- Group no.**1** will receive preoperative sublingual 400 microgram of misoprostol **(Sigma)** "2 tablets" and postoperative sublingual placebo"2 tablets".